Microbiology Question-Based Review (Micro QbR)

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Presentation Overview

- Microbiology QbR for Terminally Sterilized Products
  - purpose
  - document status
- Microbiology QbR documents for terminally sterilized products
  - QOS Outline
  - FAQ
- QbR questions, FAQs, and Responses
- Key highlights (Pharmaceutical Development and QbD concepts)
- Future Micro QbR documents

Why Microbiology QbR?

- Transparent Review Process
  - Questions posted on OGD website
  - FAQ document to provide guidance
  - Model QOS with example responses?
- Decrease deficiencies and number of review cycles
- Decrease review time???
  - Micro QOS: basis of review
- Regulatory relief (QbD)

Micro QbR Document Status

- Finalized documents:
  - **Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Quality Overall Summary Outline**
  - **Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions**
- Posted on OGD web site?

Micro QbR Approach

- Reformat 1994 Guidance topics and incorporate QbD concepts
  - "questions" rather than "statements"
  - CTD format
  - Update to include QbD and clarify/expand 1994 Guidance
- Focus on QOS
  - Essentially a "model" review
  - QOS: Basis of review

Micro QOS Outline

- Include in Module 2
- Contains the FDA “questions” and applicant “responses”
- Supplements Module 3 information
- Similar to detailed Executive Summary of Module 3
- Incorporates QbD concepts
- Optional

Examples of Micro QbR Questions: Antimicrobial Effectiveness (1)

2.3.P.2 Pharmaceutical Development

- QbR Question: Is the drug product packaged as single-use/dose, multi-dose, or pharmacy bulk?
- *FAQ: What information should be presented in this section?*
- Response:
  - Indicate single/multi-dose/pharmacy bulk
  - Indicate instructions for discard unused portion
  - Sufficient volume for multiple doses?
  - AET may be needed when no indication of single dose, no discard statement, and sufficient volume for multiple doses.

Examples of Micro QbR Questions: Antimicrobial Effectiveness (2)

- QbR Question: If the drug product (whether preserved or inherently antimicrobial) is intended for multi-dose administration, how was the antimicrobial effectiveness demonstrated for the drug product?
- *FAQ: What information should be presented in this section?*
- Response: Provide antimicrobial effectiveness testing results using the drug product formulated with the preservative or antimicrobial ingredient at or below the lowest concentration that complies with the finished product release specification or stability specification (whichever is lower).

Examples of Micro QbR Questions: Antimicrobial Effectiveness (3)

- Specify if the USP <51> method is used and, if not, describe the method.
- Include the preservative content or % label claim for the tested batch(es) and challenge organisms used.
- Provide results in table format (example table included)
- Provide the finished product release and stability preservative content acceptance criteria. If the product is inherently antimicrobial, provide the acceptance criteria for the antimicrobial ingredient(s) (e.g. API).

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (1)

2.3.P.2 Pharmaceutical Development

- QbR Question: What are the labeling instructions for reconstitution and further product dilution with regard to diluents used and storage conditions?
- *FAQ: What information should be included in this section?*
- Response:
  - Reconstitution: Identify the fluid(s) and volume (or final product concentration) used for reconstitution, and temperature/duration storage conditions for the reconstituted product.
  - Further product dilution: Identify diluent(s) and dilution volume (or dilution factor or final product concentration) and temperature/duration storage conditions for further storage (if applicable) of diluted product.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (2)

- QbR Question: If the drug product is reconstituted (or further diluted) and stored prior to administration, what studies were conducted to demonstrate that the drug product does not support microbial growth over the storage periods/conditions described in labeling?
- *FAQ: What information should be provided in this section?*

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (3)

- Response:

  Provide the following information:

  - Summary of test method
  - Challenge organisms and challenge titers
  - Product sample concentration(s) and storage conditions
  - Diluent(s) tested
  - Summary of results

  If these studies were not performed, then provide product risk assessment or scientific justification for not performing the studies. Note that simply stating that the studies were performed or should have been performed during development of the RLD is not a valid justification for not performing studies.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (4)

- *FAQ: How is "does not support microbial growth over the storage periods/conditions described in labeling" defined?*
- Response: < 0.5 log10 increase in challenge titers over incubation periods/conditions specified in labeling.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (5)

- *FAQ: What microorganisms should be tested?*
- Response: At minimum we recommend compendial organisms. Examples can be found in USP <51> and <71>.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (6)

- *FAQ: Which diluent(s), product concentration, and storage conditions(s) should be tested?*
- Response: Either test all diluents listed in labeling or a diluent considered worst case (most favorable for microbial growth) among those listed in labeling. If no diluents are specified in labeling, choose a diluent considered worst case (most favorable for microbial growth).

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (7)

- *FAQ: Should the study results meet the acceptance criteria of compendial antimicrobial effectiveness testing?*
- Response: No, a reduction in challenge organism titer is not necessary, only evidence that the drug product does not support growth.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (8)

- *FAQ: Should the RLD and proposed generic be tested side-by-side?*
- Response: We recommend that RLD and generic be tested in parallel, but parallel testing is not required. Results should meet acceptance criteria of *"does not support microbial growth over the storage periods/ conditions described in labeling" (as describe*d above) for reconstitution studies.

Examples of Micro QbR Questions: Reconstitution/Dilution/Storage (9)

- *FAQ: May sterility testing be used to demonstrate that the drug product does not support microbial growth over the storage periods/conditions described in labeling?*
- Response: No, in order to show that the drug product does not support microbial growth, product samples should be challenged with a panel of different species of microorganisms.

Examples of Micro QbR Questions: Pharmacy Bulk Packaging (1)

2.3.P.2 Pharmaceutical Development

- QbR Question: If the drug product is a pharmacy bulk product, what are the labeling instructions for product entry and dispensing?
- *FAQ: What information should be provided in this section?*
- Response: Indicate the time period for dispensing the product and the number of entries allowed.

Examples of Micro QbR Questions: Pharmacy Bulk Packaging (2)

- QbR Question: If the drug product is a pharmacy bulk package and the labeling indicates that the drug product may be dispensed over a time period greater than four hours after initial closure entry, do studies support the extended dispensing period?
- *FAQ: What type of study should be performed to support the extended pharmacy bulk dispensing duration?*
- Response: Same as above for reconstitution study.

Examples of Micro QbR Questions: Pharmacy Bulk Packaging (3)

- *FAQ: Should the RLD and proposed generic be tested side-by-side?*
- Response: We recommended that RLD and generic be tested in parallel, but do not require parallel testing. Results should meet acceptance criteria of "does not support microbial growth over the storage periods/ conditions described in labeling" (as described above) for reconstitution studies.

QbD: Design Space

- *FAQ:* How is design space defined in terms of production and validation for a terminally sterilized drug product?
- Response:
  - "Design space" as defined by ICH Q8(R1) Pharmaceutical Development is "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."
  - For example, in terms of **container/closure systems**, the design space may include materials (container and closure type and composition), dimensions and tolerances, production assembly process parameters, and production sterilization/depyrogenation conditions (parameters and limits).
  - For example, in terms of **sterilization and depyrogenation processes**, the design space may include process parameters (both validation and commercial production), sterilization and depyrogenation equipment, process limits and acceptance criteria, load sizes, and load composition.

Examples of Micro QbR Questions: Container/Closure Integrity (1)

2.3.P.2 Pharmaceutical Development

- QbR Question: How was the container/closure system for the drug product validated to function as a barrier to microbial ingress?
- *FAQ: What information should be presented in this section?*

Examples of Micro QbR Questions: Container/Closure Integrity (2)

Response:

Provide a brief description of the method, materials and container/ closure components used for the study, controls performed, acceptance criteria, results, and conclusions. The description of the method should include:

- How the test and control units were prepared
- Number of units tested
- Nature and duration of the challenge
- Any conditions applied (e.g. vacuum, pressure)
- Method of detection and sensitivity of the test
- How positive controls were prepared and challenged

The study design should address any interface that functions as a sterile barrier and ensure that the entire fluid pathway of the drug product is assessed.

Describe what measures were taken to ensure that each container/closure system used in the study was exposed to production conditions that might impact container/closure integrity, such as maximum sterilization/depyrogenation conditions.

Examples of Micro QbR Questions: Container/Closure Integrity (3)

- QbR Question: What is the container/closure **design space** and change control program in terms of validation?
- *FAQ: What information should be presented in this section?*
- Response: If the container/closure design space has been established, then describe the container/closure design space parameters (e.g. dimensions, composition, and torque range, residual seal force, storage conditions, sterilization conditions, etc.) and corresponding acceptance criteria which were validated for container/closure integrity.

  Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

Examples of Micro QbR Questions: Container/Closure Integrity (4)

- *FAQ: What if a container/closure **design space** has not been established?*
- Response: If a container/closure design space has not been established, then indicate “Not applicable” or “N/A” as the answer to this question.

  Any future changes made after the application has been approved would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

Examples of Micro QbR Questions: Manufacturing Process

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Overall Manufacturing Processes)

- QbR Question: How will the drug product manufacturing process be **designed** for commercial production?
- *FAQ: What information should be provided here?*
- Response: Provide a general summary of the manufacturing process and in-process controls from the end of compounding through terminal sterilization. Describe any steps performed to minimize bioburden prior to terminal sterilization (i.e. use of filtration and/or aseptic processing prior to terminal sterilization, component/ equipment sterilization, or use of pre-sterilized components). Indicate hold time specifications and hold conditions. Describe any routine procedures that are in place to test bioburden and/or container closure integrity during commercial production, as applicable.

Examples of Micro QbR Questions: Parametric Release

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Overall Manufacturing Processes)

- QbR question: Is parametric release in lieu of sterility testing being requested for release of the finished drug product?
- *FAQ: What information should be provided in this section?*
- Response: If this question is applicable and parametric release is being requested based on an NDA/ANDA previously approved for parametric release using the identical manufacturing facility, autoclave, container closure system, cycle process control parameters, and load patterns, indicate the NDA/ANDA number and supplement number (if applicable) for the drug product(s). Indicate the submission date(s) and approval date(s) for parametric release of the referenced drug product(s).

Examples of Micro QbR Questions: Terminal Sterilization (1)

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Terminal Sterilization)

- QbR Questions:
  - What is the **design space** of the terminal sterilization process for commercial production and what are the critical parameters of the production terminal sterilization cycle?
    - *FAQ: What information should be provided in this section?*
    - Response: Provide a description of the terminal sterilizer(s) to be used for commercial production including make, model/equipment number, and process type (saturated steam, water spray, etc.). Indicate if the process is designed as an overkill, bioburden-based, or combined bioburden/biological indicator-based process. Indicate process control parameters to be used for commercial production including time, temperature, F0, and pressure set points and acceptance criteria (including limits and ranges), as applicable.

Examples of Micro QbR Questions: Terminal Sterilization (2)

- *FAQ: What additional information should be provided if parametric release of the drug product is being requested?*
- Response: Indicate the critical parameters and acceptance criteria that must be met for commercial batch release.

Examples of Micro QbR Questions: Terminal Sterilization (3)

- What loading patterns are included in the sterilization process **design space** for the commercial terminal sterilization of the finished drug product?
- FAQ*: What information should be provided in this section?*
- Response: Describe autoclave loading patterns for commercial production, including the following:
  - Indication if the load sizes will range within defined minimum and maximum load sizes or if a fixed load size will be used
  - Number of drug product units per minimum, maximum, or fixed load
  - Arrangement of the drug product units within the load

Examples of Micro QbR Questions: Terminal Sterilization (4)

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Terminal Sterilization)

- QbR Questions:
  - How will the critical parameters of the terminal sterilization cycle/process be monitored and controlled during commercial production?
  - What is the sterilization process requalification/revalidation program?
  - Will the drug product be re-processed or re-sterilized and how has the impact of any reprocessing/ re-sterilization procedure been assessed?
  - What are the in-process microbiological controls in place for the manufacturing environment and product prior to sterilization?

Examples of Micro QbR Questions: Terminal Sterilization Process Validation (1)

2.3.P.3.5 Process Validation and/or Evaluation (Terminal Sterilization)

- QbR Questions:
  - Has the validation data provided for the terminal sterilization process in the subject ANDA been previously submitted and approved in another ANDA/ NDA?
  - How was the **design space** of the terminal sterilization process validated to demonstrate uniformity and reproducibility of heat distribution and heat penetration and how does it support the conditions and loading patterns proposed for commercial production?

Examples of Micro QbR Questions: Terminal Sterilization Process Validation (2)

2.3.P.3.5 Process Validation and/or Evaluation (Terminal Sterilization)

- QbR Questions:
  - How was the microbial efficacy of the terminal sterilization cycle **design space** demonstrated to show at least a sterility assurance level (SAL) of $1x10^{-6}$? How were these validation studies designed?

Examples of Micro QbR Questions: Terminal Sterilization Process Validation (3)

- What is the terminal sterilization **design space** and change control program in terms of validation?
- FAQ: *What information should be provided in this section?*
- Response: Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

Examples of Micro QbR Questions: Hold Time Prior to Terminal Sterilization

2.3.P.3.5 Process Validation and/or Evaluation (Hold time prior to terminal sterilization)

- QbR Questions:
  - Are there validation studies that support holding periods of the bulk solution after compounding or of the drug product after filling, but prior to terminal sterilization?
  - How were pre-sterilized bulk holding periods/conditions validated?

Examples of Micro QbR Questions: Component Depyrogenation

- *FAQ: Is component depyrogenation necessary for all terminally sterilized drug products?*
- Response: The combination of the following factors should be used in determining whether or not component depyrogenation is necessary:
  - Non-pyrogenic label claim
  - Capacity of the container/closure components to withstand depyrogenation processes
  - Component manufacturing process, component design, and depyrogenation feasibility (e.g. Blow-Fill-Seal processes)
  - Route of administration

Examples of Micro QbR Questions: Component Sterilization

- *FAQ: Is this section needed for all applications?*
- Response: No, this section applies to components such as port tube-closure assemblies for flexible containers that are sterilized separately prior to attachment to the container during manufacture. The moist heat of the terminal sterilization process may not adequately penetrate into septated compartments within the ports, resulting in dry heat conditions. As a result, any microorganism located in these areas might not be killed during the terminal sterilization process. Therefore, ancillary sterilization of port assemblies prior to attachment to the drug product container may be necessary to achieve sufficient lethality at these sites.

Examples of Micro QbR Questions: Component Depyrogenation (1)

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Component Depyrogenation)

- QbR Questions:
  - What is the **design space** of the container/closure depyrogenation process for commercial production and what are the critical parameters for each container/closure depyrogenation process?
  - How will the critical parameters of each depyrogenation process be monitored and controlled during commercial production?

Examples of Micro QbR Questions: Component Depyrogenation (2)

2.3.P.3.3 Description of the Manufacturing Process and Process Controls (Component Depyrogenation)

- QbR Questions:
  - What loading patterns are included in the **design space** for each depyrogenation process for container/closure components of the finished drug product used for commercial production?
  - What is the requalification/ revalidation program for each container/ closure component depyrogenation process?

Examples of Micro QbR Questions: Component Depyrogenation (3)

2.3.P.3.5 Process Validation and/or Evaluation (Component Depyrogenation)

- QbR Questions:
  - Has the validation data for the container/closure component depyrogenation processes provided in the subject application been previously submitted and approved in another ANDA/NDA?
  - How was the **design space** of each component depyrogenation process validated to demonstrate thermal reproducibility and uniformity and endotoxin removal, and how does it support the conditions proposed for commercial production?
  - What is the component depyrogenation change control program in terms of validation and **design space**?

Examples of Frequently Asked Questions: General (1)

- How should DMFs be referenced?
- Can a DMF submission be organized according to the QbR template for sterility assurance?
- What if the drug product is terminally sterilized by a process other than moist heat?

Examples of Frequently Asked Questions: General (2)

- Can the QbR template be used for supplemental application?
- Is Micro QbR required for ANDA submissions?
- Should separate CMC and Micro QOS documents be submitted?
- Is Micro QbR applicable to both ANDAs and NDAs?

Downgrading Supplements

- Changes within design space – reduce supplements(?), eliminate additional validation studies
- Micro QbR compatible with Draft Guidance: CMC Post-approval Manufacturing Changes Reportable in Annual Reports
  - Changes in filtration process parameters (change within validated design space)
  - Change from one qualified sterilization chamber to another (change within validated design space)
  - Change in supplier of glass vial (provided no change in critical dimensions)

Next Steps

- Post Microbiology QbR documents on OGD web site:
  - QOS Outline
  - FAQ
  - Model QOS necessary?
- Modify QbR (TS) FAQ document as more questions are submitted to OGD
- Micro QbR Workshop?
- IQP: “Procedure for Performing Microbiology Sterility Assurance Reviews using the Question-based Review (QbR) Approach”
- Develop QbR documents for drug products manufactured using aseptic processing
  - Duplication of many questions from QbR (TS) document
  - Add media fill, EM, building/facilities sections, viral clearance, etc
  - More variables, open systems
- Microbiology QbR for PET products?
- Microbiology QbR for non-sterile products?

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Questions?